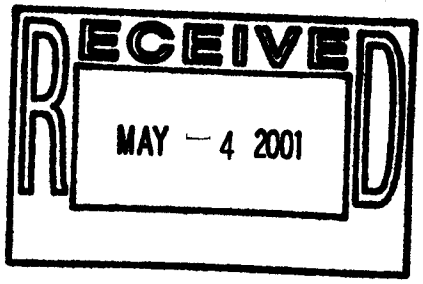
Collier Shannon Scott, PLLC
Washington Harbour, Suite 400
3050 K Street, NW
Washington, DC 20007-5108
202.342.8400 TEL
202.342.8451 FAX

John L. Wittenborn
202.342.8514
jwittenborn@colliershannon.com

Collier Shannon Scott



May 4, 2001

Via Electronic and U.S. Mail
Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: *10th Report on Carcinogens* Listing Recommendation for Metallic Nickel and Nickel Alloys

Dear Dr. Jameson:

On behalf of the Specialty Steel Industry of North America ("SSINA"), we are pleased to submit the following comments regarding the listing recommendations by the Board of Scientific Counselors ("Board") of the National Toxicology Program ("NTP") regarding "metallic nickel" and "nickel alloys" with respect to the *10th Report on Carcinogens* ("Report"). 66 Fed. Reg. 13,334 (Mar. 5, 2001). SSINA strongly supports the Board's recommendation not to list "nickel alloys" and urges NTP to make clear in the Report that nickel alloys are not associated with increased cancer risks in humans. SSINA strongly objects, however, to the recommended listing of "metallic nickel" as "reasonably anticipated" to be a human carcinogen. For the reasons detailed in our comments submitted to NTP December 1, 2000, such a listing would totally abdicate the application of sound scientific judgment in reviewing the available toxicological and epidemiological data, and ignore over 100 years of actual human experience using metallic nickel and nickel alloys with no significant adverse effects on human health.

I. BACKGROUND

SSINA is a national trade association comprised of 15 producers of specialty steel products, including stainless, electric, tool, magnetic, and other alloy steels. SSINA members account for over 90 percent of the specialty steel manufactured in the United States, and represent the largest consumers and users of nickel in the United States. As nickel is a significant alloying agent in the production of many stainless steels and other high performance alloys, SSINA members are interested in the proper characterization of this metal for potential regulatory purposes. In particular, SSINA is very concerned about the potential listing of metallic nickel and nickel alloys in the *Report on Carcinogens*, given that the available evidence demonstrates that nickel metal and alloys are safe and valuable materials and are not associated with increased incidences of carcinogenicity.

Specialty steels play an important and expanding role in the U.S. economy and touch our daily lives in a wide range of uses. They have been used safely for over 100 years and are essential in today's industrialized economy, serving critical national defense needs and applications in aerospace; aircraft; automobiles; appliances; communications, electronic, marine, and power-generating equipment; home utensils and cutlery; construction products; food and chemical processing plant equipment; and medical, health, and sports equipment. Specialty steels are valued for these uses due to their exceptional hardness, strength, and resistance to heat, corrosion and abrasion.

II. COMMENTS

A. NTP Should Adopt The Board's Recommendation Not To List Nickel Alloys And This Clear In The Report

At the December 13, 2000 public meeting, the Board made clear that the available scientific evidence provides no support for associating "nickel alloys" with cancer in humans. Not only did the Board vote to reject the proposed listing of nickel alloys by a 7 to 3 vote, but the Board took the extraordinary step of voting 9 to 1 affirmatively not to list "nickel alloys" in the Report. The Board's actions clearly indicate that it would be scientifically improper to list nickel alloys in the Report, and NTP should adopt the Board's recommendation as final.

The Board's decision not to list nickel alloys is supported by any reasonable assessment of the available scientific evidence. As detailed in SSINA's December 1 comments, listing nickel alloys as "reasonably anticipated" human carcinogens would ignore the fact that nickel alloys such as stainless steel have been used for several decades and are universally recognized as being safe for use in a wide variety of consumer products, including cookware, eating utensils, kitchen and restaurant equipment, surgical implants, *etc.* Moreover, the conclusions in the *Draft Report on Carcinogens Background Document for Metallic Nickel and Certain Nickel Alloys* ("*Background Document*") fail to reflect the application of sound scientific judgment, particularly considering that the alleged evidence of carcinogenicity in laboratory animals is associated with forms of the alloys (powder) and routes of exposure that are not relevant to humans. There is simply no evidence that nickel alloys, including nickel alloy implants, are associated with increased cancer risks. Any classification of these benign nickel alloys as carcinogens would be entirely improper.

SSINA urges NTP to make clear in the text of the Report that nickel alloys were reviewed for listing by NTP and determined not to pose an increased cancer risk to humans. This conclusion should be incorporated into an appendix to the Report similar to Appendix C of the *9th Report on Carcinogens*. Further, the decision not to list nickel alloys should be made clear in any potential listing entry for "metallic nickel" or "nickel compounds," in order to avoid any confusion with or misinterpretation of NTP's findings.

B. NTP Should Not List Metallic Nickel As A Reasonably Anticipated Human Carcinogen

Unfortunately, the Board's recommendation with respect to "metallic nickel" does not reflect the same sound reasoning as with "nickel alloys." As detailed in our December 1 comments, the listing of metallic nickel in the Report would be unreasonable for the following reasons:

(1) Associating metallic nickel with cancer ignores over a century of human experience using nickel safely; and

(2) The conclusions in the *Background Document* regarding metallic nickel fail to reflect the application of sound scientific judgment, particularly considering that the alleged evidence of carcinogenicity in laboratory animals is associated with forms of the metal (powder) and routes of exposure that are not relevant to humans.

NTP recognizes that metallic nickel and nickel alloys have been "[w]idely used in commercial applications for over 100 years." 65 Fed. Reg. at 61,354. Despite this heavy usage of nickel, the *Background Document* acknowledges that there is no sufficient evidence from humans associating nickel metal and nickel alloys with cancer. *Background Document* at 33-36. Similarly, the International Agency for Research on Cancer ("IARC") found "inadequate evidence of carcinogenicity in humans" for nickel metal and alloys, as well as metallic implants. *Id.* at 33, 35.

Given the widespread usage of nickel metal and alloys in society, if nickel metal and alloys were truly associated with an increased cancer risk, one would expect to find significant statistical evidence of carcinogenicity associated with these substances in humans. The lack of any such evidence indicates that no significant risk exists. NTP should consider this extensive human experience with nickel metal and alloys when reviewing the listing recommendation.

NTP's listing criteria incorporate the overriding principle that "[c]onclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information." NTP, *9th Report on Carcinogens* at I-2 (2000). Such relevant information includes "route of exposure." *Id.* NTP also notes that a substance is not reasonably considered to be carcinogenic in humans, despite evidence of carcinogenicity from laboratory animals, if data indicate that "the agent acts through mechanisms which do not operate in humans." *Id.* Based on the *Background Document*, however, it does not appear that NTP has applied these principles when drawing conclusions from the animal data available for nickel metal and alloys.

Humans are exposed to nickel through inhalation, ingestion, and skin contact. *Background Document* at 15. These routes of exposure, therefore, are the only meaningful exposure routes when assessing the probity of animal studies for classifying the carcinogenic potential of nickel metal. Consistent with human experience, the *Background Document* presents no animal studies that

reliably associate nickel metal with cancer via the inhalation,[1] ingestion, or dermal contact routes of exposure. *See Background Document* at 37-51.

The comments submitted by NiPERA in December 2000 provide a thorough examination of the available human and animal data cited in the *Background Document,* and are hereby incorporated into these comments. In summary, the NiPERA comments demonstrate that:

- Data from humans show no causal relationship between exposure to metallic nickel and increased incidences of cancer;
- The only animal studies that show evidence of tumorigenic responses involve routes of exposure that are not relevant to humans, and often involve animals that experienced high toxicity during the study;
- There is no evidence of carcinogenicity from human or animal studies involving exposure to metallic nickel via inhalation, ingestion, or dermal contact -- the only relevant routes of exposure for humans; and
- Mechanistically, nickel metal is unlikely to be an effective respiratory cancer initiator.

Accordingly, applying sound scientific judgment and considering all the relevant factors, especially route of exposure, there is no basis for listing metallic nickel as "reasonably anticipated" to be a human carcinogen.

C. NTP Must Make Clear That The "Metallic Nickel" Listing Does Not Include Other Forms Of Nickel

If NTP proceeds with listing "metallic nickel" as a "reasonably anticipated" human carcinogen, it should carefully identify the specific Chemical Abstracts Service ("CAS") number for the substance being listed, presumably "nickel (CAS No. 7440-02-0)." The vast majority of studies reviewed by NTP show no association of cancer with nickel alloys, numerous nickel compounds, and other forms of nickel. In SSINA's opinion, it would be improper and scientifically incorrect to list "metallic nickel" at all. It would be even more arbitrary and unreasonable if any such listing applied to any form of nickel other than *pure* nickel (CAS No. 7440-02-0).

---

[1]The one cited inhalation study that indicated a tumorigenic response via inhalation (Hueper 1958) involved extraordinarily high levels of nickel (15 mg/m^3 administered for six hours per day for four or five days per week over 21 months) and resulted in high mortality rates among the subject guinea pigs. In contrast, the three other cited studies revealed no tumorigenic responses.

To avoid confusion and improper interpretation by users of the Report, the parameters of the "metallic nickel" listing should be clearly defined. The failure to do so would have significant and unwarranted regulatory and economic repercussions for manufacturers and users of nickel-based products, including stainless steel and other nickel alloys for which the NTP Board has found not to be associated with increased cancer risks to humans. As discussed above, the entry for "metallic nickel" must make clear that "nickel alloys" are not considered to pose a carcinogenic risk to humans and are not encompassed by the listing.

III. CONCLUSION

Based on the foregoing, SSINA believes that the Board's recommendation not to list "nickel alloys" should be adopted by the NTP. Further, NTP should affirmatively state in the text of the Report that nickel alloys were reviewed for listing but that the evidence did not demonstrate that they pose an increased risk of cancer in humans. SSINA also strongly objects to the Board's recommendation that "metallic nickel" should be listed as a "reasonably anticipated" human carcinogen. The recommendation is unsupported by the available evidence, contrary to sound scientific judgment, and at odds with decades of safe human experience with nickel metal. If NTP insists on moving forward with the "metallic nickel" listing, SSINA urges NTP to make clear that the listing only encompasses pure nickel and not other forms of nickel, including nickel alloys.

The evidence is clear that metallic nickel and nickel alloys, especially stainless steels, do not pose a cancer risk to humans. Any conclusion that would associate metallic nickel and nickel alloys with increased cancer risk would be legally and scientifically unsupportable. NTP decisions have significant downstream regulatory and economic impacts. Moreover, identification as a carcinogen by NTP -- or other agency classification decisions based on NTP conclusions -- has widespread social and economic impacts (*e.g.*, toxic tort litigation, consumer product deselection). Accordingly, NTP has a legal duty to ensure that its decisions are based on sound science and the product of reasoned decision making before stigmatizing a substance as a known or reasonably anticipated carcinogen. The available evidence for metallic nickel and nickel alloys in particular does not meet this standard.

If you have any questions or we may be of any further assistance, please do not hesitate to contact us.

Very truly yours,

John L. Wittenborn
Joseph J. Green
Counsel to the Specialty Steel Industry
of North America